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Diagnosis of Intracerebral Hemorrhage with Transcranial Ultrasound

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Key Words

Acute stroke diagnosis · Intracerebral hemorrhage · Echo contrast agents · Transcranial Doppler ultrasound · Ultrasound diagnosis

Abstract

In acute stroke, different sonographic methods can be used to assess structural and hemodynamic compromise. Structural abnormalities of brain parenchyma such as primary intracerebral hemorrhage (ICH) and epiphenomena such as midline shift can be detected by native transcranial B-mode ultrasound. Moreover, transcranial Doppler provides a functional approach to intracranial hemodynamics and may assist in predicting ICH growth and global intracranial pressure increase. New ultrasound technologies allow the visualization of ultrasound contrast agents in the cerebral microcirculation. According to recent data, ultrasound perfusion imaging provides additional information for the diagnosis of ICH and may differentiate ischemic from hemorrhagic stroke. This review summarizes the impact of these different transcranial ultrasound methods on diagnosis and monitoring of ICH.

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Introduction

In acute stroke, a variety of sonographic methods providing both morphological and functional information can be used to assess the underlying pathophysiology. Transcranial Doppler (TCD), native B-mode ultrasound and contrast-enhanced techniques are eligible, and these diagnostic tools may be combined in a multimodal approach.

Primary intracerebral hemorrhage (ICH) is the etiology of 5–15% of all strokes. With a 30-day mortality of 25–43%, it has a worse prognosis compared with strokes of ischemic etiology (5–26%) [1–5]. Since reliable clinical markers are not available to differentiate between ischemic and hemorrhagic stroke in the individual patient, brain imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI) are mandatory in the acute setting [6]. Today, when a patient is referred to the emergency department with clinical signs of acute stroke, CT or MRI is routinely performed directly after admission. These well-established imaging methods can also be used for monitoring of early ICH progression or hemorrhagic transformation (HT) after thrombolysis. Nonetheless, CT and MRI require patient transportation and have other limitations such as exposure to radiation or patients with cardiac pacemakers. To date, there is still no method available allowing early diagnosis outside hospitals or systematic bedside monitoring of ICH and after cerebral ischemia. This might become the domain of transcranial ultrasound.

Pathological structures within the adult brain parenchyma such as primary ICH, midline shift after space-occupying stroke, and brain tumors can be detected by native transcranial B-mode ultrasound [7–12]. Moreover, new ultrasound technologies allow the visualization of

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ultrasound contrast agents in the cerebral microcirculation. The high diagnostic potential of these new applications for the assessment of perfusion deficits in acute ischemic stroke has been demonstrated in several recent studies [13–15].

Being still the most widespread application of transcranial ultrasound, the analysis of cerebral macrocirculation using Doppler and duplex technology has been an important tool in ischemic stroke diagnostics for more than two decades [16–18]. Analysis of TCD ultrasound spectra has an additional diagnostic value in conditions of increased intracranial pressure (ICP) showing a characteristic pattern of decreased end-diastolic flow velocity (EDV) and increased Pulsatility Index (PI) [19, 20]. Despite its widespread availability and practicability, there have been only few reports on TCD monitoring in ICH.

This review aims at characterizing the impact of different transcranial ultrasound methods for the diagnosis of primary ICH and secondary HT.

Role of TCD in Diagnosis and Monitoring of ICH

ICH lesion volume represents the most relevant predictor of outcome [21]. However, other critical aspects of the pathophysiological cascade can complicate primary hemorrhage. Hematoma growth, perilesional edema, perilesional ischemia, hydrocephalus and intraventricular hemorrhage may lead to an increase in ICP and a reduction in cerebral perfusion pressure [22]. TCD has been widely used as a tool to indirectly measure ICP. Increased ICP can affect the TCD waveform of the major intracranial arteries by decreasing flow velocity particularly during the diastole (EDV), thus increasing the PI. The PI was introduced in 1974 by Gosling and King and represents a parameter to describe and quantify the relationship between systolic and diastolic flow velocity [23]. Together with the Resistance Index (RI), introduced by Pourcelot in 1974 [24], the PI provides a measure of cerebral microvascular resistance. Many studies have confirmed the correlation of resistive indices with ICP and cerebral perfusion pressure in conditions of increased ICP [25, 26].

The value of these TCD-derived parameters for monitoring ICH has also been investigated previously. Mayer et al. [27] studied 30 patients with spontaneous supratentorial ICH and described the behavior of TCD parameters from both middle cerebral arteries (MCAs) in a lesion volume-dependent manner. They hypothesized that the critical hematoma volume beyond which hemodynamic TCD parameters, in particular PI, significantly changed was 25 ml. Martí-Fàbregas et al. [19] reported in a study of 48 patients with supratentorial spontaneous ICH that – although similar PI values were recorded from the MCA of affected and contralateral hemispheres – only the latter was an independent predictor of survival. A PI value from the MCA of the unaffected hemisphere above 1.75 accurately predicted death at 30 days with a sensitivity of 80% and a specificity of 94%. This contralateral PI increase was interpreted as a marker for a failure of compensative mechanisms to increased ICP (fig. 1). In a second study of the same group, a positive correlation between TCD parameters and ICH total volume and hypo-attenuating volume surrounding the hematoma on CT was reported [20]. In particular, an increase in PI from both hemispheres and a decrease in EDV significantly correlated with ICH volume on CT.

Klingelhöfer and Sander [28] evaluated TCD vasomotor reactivity studies in conditions of increased ICP. In patients with severe ICH, the authors reported an indirect correlation between ICP, CO_2 vasomotor reactivity and clinical outcome: the majority of patients with preserved CO_2 vasomotor reactivity showed a good recovery, while it had been impaired in patients who died during the observation period. Thus, CO_2 vasomotor reactivity as assessed by TCD may represent another relevant hemodynamic parameter for ICH monitoring.

Transcranial B-Mode Ultrasound of ICH

A-mode sonography of intracranial space-occupying processes was the first implementation of ultrasound in diagnostic medicine [29]. In infants, transcranial ultrasound is considered a standard diagnostic tool for brain imaging due to excellent insonation conditions [30, 31]. However, this method is limited in the adult brain by inadequate ultrasonic penetration of the skull in up to 18% of subjects [32, 33]. Thus, since its development in the early 1970s, CT has become gold standard for detection of acute ICH [34]. Today, MRI techniques are being judged to be at least equivalent [35] and both methods are utilized depending on clinical questions, availability, cost effectiveness and contraindications. Although these methods can nowadays be performed easily and quickly, their application is still demanding in critically ill or restless patients and in-hospital transportation is mandatory. In these situations, particularly for serial follow-up studies, transcranial ultrasound may be an alternative since it can be performed at bedside and is well tolerated.

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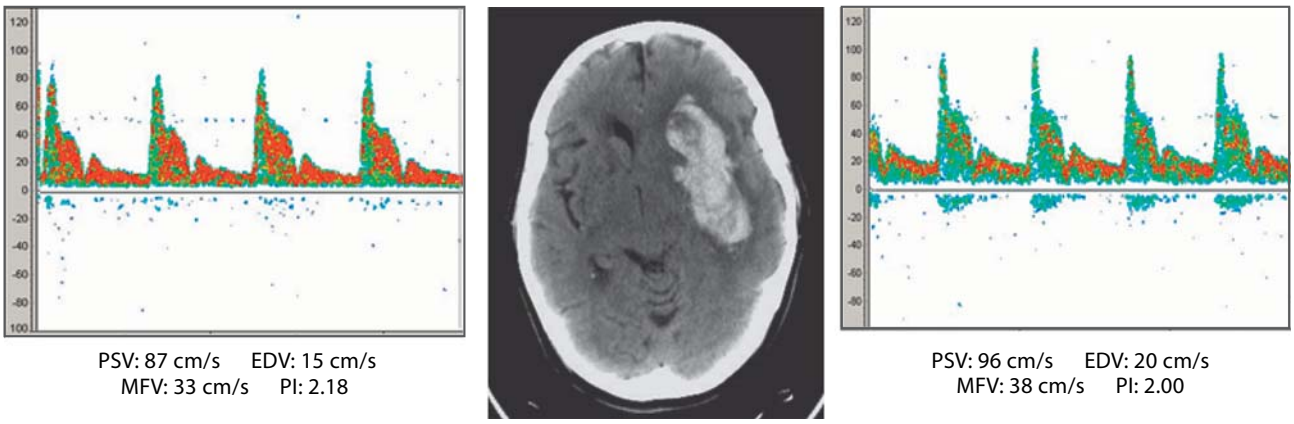

Fig. 1. A 76-year-old patient with left large supratentorial ICH and mild midline shift on CCT scan (middle). Doppler spectra from the MCA of both hemispheres (left and right) demonstrate bilateral high values of PI. The increase in PI in the MCA contralateral to the hemorrhage may be interpreted as an indicator of poor clinical outcome. PSV = Peak systolic velocity; MFV = mean flow velocity.

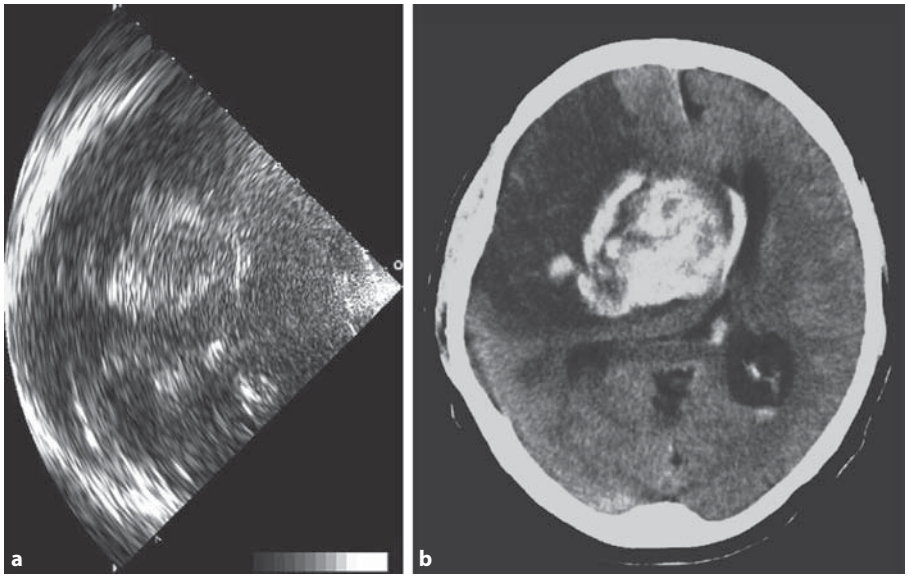

Fig. 2. A 69-year-old man with acute MCA infarction of the right hemisphere who woke up with symptoms (NIHSS 19). Transcranial color-coded duplex ultrasound revealed MCA main-stem occlusion (recanalization on day 5). On day 6, clinical deterioration occurred with stupor. Transcranial ultrasound (**a**) in standard axial investigation plane shows massive HT with midline shift as confirmed later by CCT (**b**).

Transcranial ultrasound should be performed using low-frequency (1–3 MHz) sector scanners via the transtemporal bone window. Standardized investigation planes have been established [36]. Becker et al. [9, 37] were the first to describe the utility of transcranial ultrasound in a considerable number of patients with ICH. In the acute phase, ICH appears homogenous, sharply demarcated and hyperechogenic (fig. 2). In 1993, Seidel et al. [7] were able to diagnose and localize ICH with ultrasound in 18/23 patients (78%). Insufficient insonation conditions impeded diagnosis in 13%. Evaluating serial investigations, they were the first to describe an alteration of the sonographic appearance of intracerebral hematomas over time with a decrease in echo intensity beginning at the center of the lesion.

Mäurer et al. [10] published the largest study on transcranial B-mode ultrasound in stroke patients aiming at differentiating between ischemic and hemorrhagic stroke.

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They investigated 151 patients with acute hemiparesis in a prospective study. 60 patients suffered from ICH and 67 patients had ischemic stroke. In 24 patients, CT revealed neither bleeding nor ischemia. 12% had an insufficient temporal bone window for transcranial insonation. Transcranial ultrasound differentiated correctly between ischemia and hemorrhage in 95%. Three atypical bleedings (two in the upper parietal lobe) were missed by ultrasound. In 4 patients, transcranial ultrasound provided false-positive results.

In 2006, Niesen et al. [38] published a study on transcranial ultrasound in subdural hematoma. Using transcranial ultrasound, the lesion could be detected in 22 of 25 patients with confirmed subdural hematoma (88%). In 3 patients, the temporal bone window was insufficient. The diameter of subdural hematoma as measured with ultrasound correlated well with CT findings.

Sonographic Diagnosis of HT

The development of HT after ischemic stroke is a well-known phenomenon. It represents an almost natural event in the pathophysiologic cascade of cerebral infarction. HT is not necessarily associated with clinical deterioration and may therefore remain unrecognized in routine stroke management. The impact of HT on clinical outcome remains controversial [39–43]. However, information on HT is crucial in various decisions during the acute phase of stroke management such as anticoagulation therapy.

In an early study on acute hemispheric stroke patients, transcranial ultrasound showed high sensitivity (90%) and specificity (97.1%) in depicting HT [44]. In 10 of 11 patients with HT as diagnosed by CT, the lesion was correctly identified by transcranial ultrasound. Identification of HT failed in one patient suffering from a small hemorrhage in the parietal lobe with a diameter of less than 1 cm. In another patient, transcranial ultrasound provided a false-positive result. There was an increase in echogenicity over time that was interpreted as probable stepwise evolution of HT. In a recent study, the usefulness of transcranial ultrasound for HT monitoring could be confirmed: in 62.5% of 19 patients treated with tPA, HT was observed in the first 60 h after symptom onset [45]. The proportion of patients with HT who did not receive tPA treatment was 33.3%. In 20 of 55 patients, CT revealed HT of infarction and transcranial ultrasound detected 18 of 20 HTs in the symptomatic hemisphere (90%). In one patient, transcranial ultrasound provided a false-positive result because of a reverberation artifact; in 2 patients, a small cortical HT was missed (sensitivity 90.0%, specificity 97.1%).

Value of Echo Contrast Agent Microbubbles for ICH Assessment

An important milestone for ultrasound imaging has been the introduction of echo contrast agents. They contain microbubbles of a specific gas supported by a carrier particle or encapsulated in various types of shells. Echo contrast microbubbles are able to survive the pulmonary and capillary transit, distribute uniformly in the arterial microcirculation and produce a detectable echogenic response in vessels and tissue. The first generation of echo contrast agents containing air-filled microbubbles (e.g. Levovist®) has mostly been replaced by newer synthetic agents (e.g. SonoVue®, Optison®). These agents show superior characteristics such as a better stability and longer half-life [46–49]. Echo contrast agents strongly increase the acoustic backscatter in arteries and veins and they can therefore be used to improve the quality of vascular ultrasound imaging. In neurosonology, echo contrast agents also allow evaluation of the major intracerebral arteries in difficult insonation conditions [50]. Echo contrast agents are the most important requirement for ultrasound perfusion imaging (UPI).

UPI utilizes a contrast-specific imaging mode for visualization of microbubble-related backscatter that is based upon the nonlinear behavior of microbubbles to acoustic waves. Pulse inversion harmonic imaging transmits two pulses at a fundamental frequency and uses the second harmonic component of the backscattered echoes to form an image. Due to the different responses to echoes – bubbles respond with nonlinear oscillations and tissue mostly generates linear backscatter – fundamental echoes from tissue can be cancelled, leaving only signal arising from the contrast agent. UPI is widely used in medicine, e.g. in myocardial, renal and musculoskeletal tissue, whereas this approach is more challenging in the human brain due to the attenuation of the skull bone. Nevertheless, UPI has shown to be useful in many conditions of disturbed cerebral hemodynamics related to brain infarction or brain tumors [13–15, 51–54].

We have recently performed a first study evaluating the impact of UPI in 12 patients with CT diagnosis of acute supratentorial ICH [55]. Native transcranial B-mode ultrasound and UPI with echo contrast agents (Sonovue) were performed on day 1 and on days 5–7 includ-

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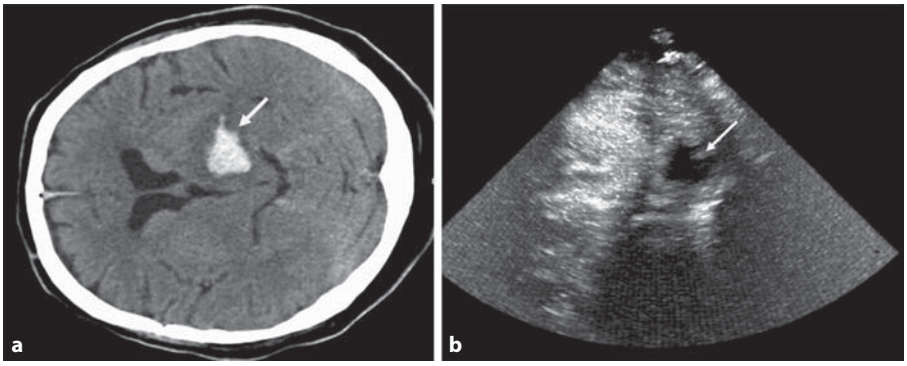

Fig. 3. a Example of a 65-year-old patient with primary ICH (arrow) in the left thalamus as detected by CCT. **b** Using UPI, the ICH lesion is clearly delineated from adjacent tissue due to the focal absence of microbubble enhancement.

ing ICH volume measurements using the maximum extension on transverse and coronal ultrasound planes. ICH was identified as hyperechogenic mass on native B-mode ultrasound in 11/12 patients, but the correlation with CT volume measurements was poor. Volume measurement was more precise using UPI (day 1: $r = 0.8$, 95% CI: 0.47–0.94, $p < 0.001$; days 5–7: $r = 0.94$, 95% CI: 0.81–0.98, $p < 0.001$). Using UPI, the typical finding was a focal reduction in contrast agent arrival in the ICH core, which led to better delineation of the lesion borders from adjacent tissue. Depiction of lobar ICH was difficult with ultrasound, and lesion sizes tended to be underestimated. This study supported earlier work that had already demonstrated the usefulness of native transcranial B-mode ultrasound for the diagnosis of ICH [7, 9, 10]. However, sonographic measurements of ICH lesion volumes – needed for monitoring purposes and quantitative volume follow-up – were more precise using UPI due to the characteristic reduction in contrast arrival in the core of the lesion (fig. 3). On parametric UPI maps, the discrimination of lesion borders from adjacent tissue was clearly visible even under difficult insonation conditions, e.g. tissue echolucency in patients with white matter disease.

Similar results were reported from a UPI study by Vicenzini et al. [54]. They examined 20 patients with space-occupying brain lesions, 4 of them having ICH. Contrast enhancement was absent in all cases with ICH and very high in glioblastomas and meningiomas.

Within the framework of the EU-funded research project UMEDS (Ultrasonographic Diagnosis and Monitoring of Stroke), a prospective multicenter study has recently been performed to determine sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of transcranial ultrasound for the diagnosis of acute ischemic stroke versus ICH within 24 h from onset [56]. 33 acute stroke patients (10 females, 23 males, mean age 68 years) were included in three German stroke centers (Mannheim, Bochum and Lübeck) after abrupt onset (mean 13 h) of a focal neurological deficit suggestive of supratentorial stroke. Transcranial ultrasound imaging studies were performed by an expert investigator unaware of neuroimaging findings including transcranial color-coded duplex ultrasound, native B-mode ultrasound and UPI. Stroke (mean NIHSS = 11) was classified as ischemic in 23 patients (60%); 10 patients had ICH. Ischemic stroke was diagnosed correctly with ultrasound in 22/23 patients (sensitivity 95.7%, specificity 90%, PPV 95.7%, NPV 90%). ICH was detected with a sensitivity of 80% (specificity 100%, PPV 100%, NPV 92%). UPI revealed hemodynamic impairment in patients showing a perfusion deficit on MRI with a sensitivity of 80%, a specificity of 100% and a PPV of 100%, whereas NPV was low (50%). This prospective multicenter study was the first to provide information on the diagnostic validity of transcranial ultrasound including UPI performed by a blinded investigator in acute ischemic stroke versus ICH.

Safety Aspects

The interaction of ultrasound pulses with microbubbles may produce mechanical perturbation and a potential for negative effects on nearby cells or tissues. In the skeletal muscle and the myocardium, bioeffects reported for mechanical index values greater than 0.4 include microvascular leakage, petechiae, cardiomyocyte death, inflammatory cell infiltration, and premature ventricular contractions [49]. Only few data are available on bioeffects of transcranial ultrasound in combination with microbubbles in the cerebral parenchyma; however, there has been some discussion whether this combination may also cause capillary ruptures that might lead to bleeding

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or opening of the blood-brain barrier [57]. These concerns have been addressed by more recent work in rabbits showing that current diagnostic ultrasound exposure levels combined with microbubbles are below the threshold of blood-brain barrier opening or brain tissue damage [58]. Correspondingly, MRI studies of humans provided safety data of contrast agents at exposure levels of current ultrasonic equipment used for transcranial investigations without evidence of adverse effects [59, 60].

We have recently studied the effects of simultaneous application of ultrasound and microbubbles in rat models of ICH and cerebral ischemia [61, 62]. In this experimental setting using peak negative pressures and spatial peak-temporal peak intensities that are much higher than the ultrasound intensities achieved in clinical studies, we still found no adverse effect on the brain as compared with controls. In addition, our recent clinical studies did not reveal any safety concerns in ICH patients who underwent UPI. The rate of ICH progression was similar to what was expected in this clinical entity [4, 5]. Nevertheless, safety concerns related to echo contrast agents have still to be addressed for human studies and further research on this topic is needed.

Future Perspectives

Insufficient insonation conditions in about 15% of patients are the major limitation of transcranial ultrasound. However, the ultrasound probes currently used in clinical routine are not specifically designed for transcranial ultrasound. Indeed, they are not optimized for lower frequencies and higher mechanical index imposed by the attenuation from the skull. A potential improvement may therefore be the construction of ultrasound probes which were developed for brain imaging. Technical solutions for correction of skull irregularities are currently under investigation [63]. Moreover, 3-D techniques and computer-aided image analysis might reduce the dependence of the method on investigators' skills [64–66], and 3-D ultrasound probes may also increase the diagnostic window from the transtemporal approach.

Targeted echo contrast agents may be another approach to improve diagnostic confidence and might be useful in ICH or HT patients. Ligands such as antibodies, antigen-binding antibody fragments or synthetic peptides attached to the microbubbles specifically bind at the target tissue to selectively enhance it. This 'molecular imaging' may have the potential to become a valuable tool in stroke diagnostics and therapy. In particular, the use of specifically targeted contrast agents that have the potential to adhere to thrombus material [67, 68] may have therapeutic implications such as site-specific thrombolysis. Molecular imaging may also play a role in ICH diagnosis by improving either detection of the hematoma itself or of the concomitant inflammation reaction.

Conclusions

Previous studies have indicated that TCD-derived parameters such as the PI of both hemispheres and TCD assessment of CO_2 vasomotor reactivity may be useful in the diagnosis of ICH. TCD may assist in predicting hematoma growth, global ICP increase and prognosis. In particular, a PI increase in the contralateral hemisphere seems to correlate with poor outcome. Transcranial B-mode ultrasound can detect ICH and HT directly with a high sensitivity and specificity. Nonetheless, the current diagnostic accuracy seems to be insufficient to support therapeutic decisions in the first line. Limitations are insufficient temporal bone windows in a considerable number of patients, the inability of transcranial ultrasound to diagnose lesions in the upper part of the frontal and parietal lobes as well as its limited spatial resolution. Sonographic discrimination between HT and ICH is not feasible [45]. Thus, the most important application of transcranial ultrasound remains bedside monitoring, once the insonation conditions have proved sufficient. According to recent studies, UPI provides valuable additional information for the diagnosis of ICH and may differentiate ischemic from hemorrhagic stroke. Due to the typical reduction in contrast enhancement, UPI parametric images provide good estimates and improved volume measurements compared with B-mode ultrasound alone in ICH patients. If confirmed in larger patient series, UPI might be used on Stroke Units for monitoring ICH progression or regression.

Transcranial ultrasound techniques, both established and new, offer a variety of promising diagnostic bedside approaches to the critically ill patient with ICH. Larger blinded studies are desirable to evaluate the diagnostic impact of this method.

Disclosure Statement

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